184 ADOPTIVE T CELL THERAPIES TARGETING COMMON P53 NEOANTIGENS IN HUMAN SOLID CANCERS

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Background Adoptive cell therapies (ACT) targeting neoantigens arising from somatic mutations in cancer cells can successfully treat advanced solid cancers. Most neoantigens are rare and targeting them via ACT would require highly individualized therapies. Instead, we focused on p53 mutations shared among a broad range of patients. In this study, we have identified tumor infiltrating lymphocytes (TILs) and T cell receptors (TCR) recognizing p53 mutations and evaluated the efficacy of ACT targeting p53 neoantigens.

Methods Patient TILs were screened for reactivity against p53 mutations. Twelve patients with positive p53 neoantigen screening received autologous TIL ACT. One patient received TCR-engineered peripheral blood lymphocytes (PBL) ACT.

Results From 77 patient samples, TILs recognizing both 'hotspot' and 'non-hotspot' p53 mutations were detected in 21 patient TILs (table 1). ACT using an HLA-A*02-restricted TCR targeting p53(R175H) led to regression of TYK-nu ovarian cancer cells that were p53(R175H)+ and HLA-A*02+ in NSG mice. Treatment of 12 patients with chemo-refractory epithelial cancers with autologous TILs targeting p53 neoantigens resulted in limited clinical responses (2 partial responses). We detected low frequencies, exhausted phenotypes, and poor persistence of the infused mutant p53-reactive TILs (table 2). Alternatively, we engineered peripheral blood lymphocytes (PBL) to express anti-mutant p53 TCRs. We retrovirally expressed the HLA-A*02:01-restricted anti-p53(R175H) TCR that had been tested preclinically in patient 4349's autologous PBL. This approach improved anti-mutant p53 TCR expression and T cell persistence relative to the autologous TIL treatments. Patient 4349 with chemo-refractory breast cancer received 5.3e10 cells and, at 14-weeks post-ACT, she experienced significant regression of the metastases in the pericardium and chest wall, as well as the subcutaneous tumor deposits based on RECIST criteria (down 55%). Single cell RNA sequencing of PBLs at 6 weeks post-ACT revealed a cluster of circulating T cells with a central-memory and stem cell-like phenotype that expressed SELL (CD62L), IL7R, TCF7 (TCF1) and LEF1, suggesting long-term immunity against the p53 neoantigen. The patient recurred at 6 months post-ACT with a metastasis that exhibited loss of heterozygosity of a portion of chromosome 6 that included HLA-A*02.

Conclusions We have established a library of anti-mutant p53 TCRs that could potentially be used to treat 7.3% of patients with solid cancers that express the corresponding p53 mutation and HLA. One breast cancer patient treated with TCR-engineered PBLs targeting p53R175H experienced an objective response lasting 6 months. Collectively, our data demonstrate the feasibility of targeting shared p53 neoantigens by ACT for the treatment of solid cancers.

Abstract 184 Table 1 Anti-mutant p53 TCR library

TCR source	*TP53* mutation	*TP53* mutation frequency (%)[a]	HLA restriction	HLA frequency (%)[b]	Potentially treatable patient (%)
4141; 4196	R175H	5.530	A*02:01	47.40	2.621
4273	R248W	3.218	DPB1*02:01	27.30	0.878
4259	Y220C	1.790	A*02:01	47.40	0.848
4149; 4343	Y220C	1.790	DRB3*02:02	32.80	0.587
4285	R175H	5.530	DRB1*13:01	10.00	0.553
4386	R273C	2.259	DPB1*04:02	24.2[c]	0.547
4127	G245S	1.598	DRB3*02:02	32.80	0.524
4259	Y220C	1.790	DRB1*04:01	17.30	0.310
4266	R248W	3.218	A*68:01	6.38	0.205
4316	C135Y	0.426	DRB1*07:01	26.84	0.114
4304	M237I	0.426	DRB1*01:01	14.60	0.062
4316	C135Y	0.426	A*29:02	7.06	0.030
4350	L111R	0.011	A*11:01	60% in Chinese populations	0.006
4324	T211I	0.032	C*06:02	18.64	0.006
4414	Y220D	0.011	A*02:01	47.40	0.005
4114	C135R	0.043	DRB1*11:01	10.9	0.005
4350	L111R	0.011	DRB1*08:03	7-20% in Chinese populations	0.004
4356	Q331H	0.011	B*40:01	11.00	0.001
4293	Y236S	0.011	DRB3*02:01	0.33	0.00003
Sum					7.305

Abstract 184 Table 2 Characteristics of 12 TIL and 1 TCR-engineeredACT

Patient ID	Tumor type	p53 mutation	Protocol	HLA restriction	Number of IL2	Number of pembrolizumab	% mut-p53 reactive cells in infusion product[a]	Total number of cells given to patients	Number of mutant p53 reactive cells given to patients	% persistence at 6 weeks post-ACT[a]	% PD1$^+$ in infusion product	% TIM3$^+$ in infusion product	% CD39$^+$ in infusion product	% CD62L$^+$ in infusion product	Response (months)
4114	Pancreatic	C135R	Selected TIL (NCI-10-C-0166)	DRB1*11:01	2	0	18.9	2.14E+10	4.04E+09	Not detected	43.1	28.5	15.83	20.92	NR
4127	Ovarian	G245S	Selected TIL (NCI-10-C-0166)	DRB3*02:02	5	2	2.8	1.43E+11	4.00E+09	Not detected	16.66	33.83	71.8	15.94	PR (4)
4141	Colon	R175H	Selected TIL (NCI-10-C-0166)	A*02:01	4	4	2.2	6.90E+10	1.52E+09	0.05	46.2	32	87.4	29.24	NR
4149	Ovarian	Y220C	Selected TIL (NCI-10-C-0166)	DRB3*02:02	5	4	11.1	3.71E+10	4.12E+09	Not detected	58.7	15.27	93.2	6.8	SD (5)
4196[c]	Colon	R175H	Selected TIL (NCI-10-C-0166)	A*02:01	0	4	3.3	9.18E+10	3.03E+09	0.02	NA	NA	NA	NA	SD (3)
4266	Colon	R248W	Selected TIL (NCI-10-C-0166)	A*68:01:02	6	0	50.8	1.01E+11	5.13E+10	0.19	64	89.5	98.8	0.89	NR
4273	Rectal	R248W	Selected TIL (NCI-10-C-0166)	DPB1*02:01:02	2	2[e]	6.75	1.17E+11	7.90E+09	NA	28.4	42.7	96.3	4.03	NR
4285	Colon	R175H	Selected TIL (NCI-10-C-0166)	DRB1*13:01:01	6	0	2.43	6.96E+10	1.69E+09	Not detected	55.9	56.5	76.11	2.08	NR
4304	Colorectal	M237I	Selected TIL (NCI-10-C-0166)	DRB1*01:01	4	4	13 (3 TCRs)	8.97E+10	1.17E+10	0.01	30.6	19.32	97.4	2.79	NR
4324	Colorectal	T211I	Selected TIL (NCI-10-C-0166)	C*06:02	3	4	45 (2 TCRs)	8.49E+10	3.82E+10	1.45	29.8	75.7	29.8	5.02	SD (3)
4343	Breast	Y220C	Selected TIL (NCI-10-C-0166)	DRB3*02:02	4	4	1[d]	7.68E+10	7.68E+08	0.002	63.2	NA	97.1	9.73	PR (6)
4350	Colon	L111R	Selected TIL (NCI-10-C-0166)	A*11:01 DRB1*08:03	5	2	11	6.69E+10	7.36E+09	0.115	30.9	3.37	94.2	3.37	NR
4349	Breast	R175H	Allogeneic R175H TCR (NCI-18-C-0049)	A*02:01	0	1[e]	64[b]	5.30E+10	3.39E+10	14.4[b]	13	21.7	52	51.5	PR (6)

Ethics Approval This study was approved by the Investigational Review Board at the National Cancer Institute in accordance with an assurance filed with and approved by the U.S. Department of Health and Human Services and was registered at https://clinicaltrials.gov under NCT00068003, NCT01174121 and NCT03412877.

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